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PLASMA ADIPONECTIN CONCENTRATIONS IN NON PREGNANT, NORMAL PREGNANCY AND OVERWEIGHT PREGNANT WOMEN

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Abstract

Aims—Adiponectin is an adipokine that has anti-diabetic, anti-atherogenic, anti-inflammatory and angiogenic properties. This hormone has been implicated in both the physiological adaptation to normal pregnancy and obstetrical complications. The aims of this study were to determine normal maternal plasma concentrations of adiponectin throughout gestation and to explore the relationships between plasma adiponectin concentration, pregnancy, and maternal overweight.

Study design—A cross-sectional study was designed to include normal pregnant women (normal weight and overweight; 11–42 weeks of gestation), and non-pregnant women. Plasma adiponectin concentration was determined by immunoassay. Non-parametric statistics were used for analysis.

Results—(1) Adiponectin was detectable in the plasma of all patients; (2) there was no significant difference in the median adiponectin concentrations between pregnant and non-pregnant women; (3) plasma adiponectin concentrations were negatively correlated with gestational age only among normal weight pregnant women; and (4) overweight patients had significantly lower adiponectin concentrations than normal weight women.

Conclusion—Consistent with the increased insulin resistance and weight gain that occur in pregnancy, adiponectin concentrations were negatively correlated with gestational age. The results of this study and the nomogram herein presented can serve as the basis to explore the relationship between adiponectin and pregnancy complications and facilitate the clinical use of this important adipokine.

Condensation—Plasma adiponectin concentrations decrease with advancing gestational age only in nonobese women.

Keywords

Adipokines; adiponectin; nomogram; obesity; pregnancies

Introduction

During the last decade, evidence has accumulated, demonstrating that adipose tissue is an important endocrine organ involved in metabolism [38,47,51,52,72,75,93,100,106]. Adipose tissue can exert its effects through several mechanisms, the most important of which is the secretion of bioactive mediators from adipocytes and other cells. These bioactive substances, collectively termed “adipokines” include: leptin [28,31,32], adiponectin [2,7,49,50,71], resistin [4,42,57,65,101], tumor necrosis factor- α (TNF- α) [43,108], Interleukin-6 (IL-6) [109,110] and others [8,65,83,93,94], and they have been implicated in the pathophysiology of insulin resistance [14,60,67,73,92,99,102], hyperlipidemia [29,107], obesity [27,62,119], inflammation [82,105,120], atherosclerosis [79–81] and the metabolic syndrome [35,70].

Adiponectin is the most abundant gene product in adipose tissue and accounts for 0.01% of total plasma protein. This is a 30-kDa molecule that has been identified independently by four groups in 1995 and 1996 with different experimental methods [46,69,76,97]. Adiponectin is produced abundantly by adipose tissue and circulates at relatively high concentrations ($\mu\text{g/mL}$) [1,9,46,56,119,120]. In contrast to other adipokines (e.g. leptin, TNF- α , and IL-6) and, although it is secreted by adipocytes, adiponectin plasma concentrations are paradoxically lower in obese subjects than in non-obese subjects [2,46]. Weight reduction in obese individuals is accompanied by an increase in plasma adiponectin concentration [27,119], suggesting that adipose tissue can exert a negative feedback on adiponectin production or secretion.

There is evidence to support the insulin-sensitizing properties of adiponectin: (1) an inverse correlation exists between insulin resistance indices and plasma adiponectin concentrations in humans [44,111]; (2) A locus on chromosome 3 (3q27), linked to type 2 diabetes, includes the adiponectin gene [39,61] and single nucleotide polymorphisms in the adiponectin gene have been associated with a high risk of type 2 diabetes [123]; and (3) administration of adiponectin to normal or obese mice improves glucose tolerance and insulin sensitivity [6,33,118]. In addition to its role in glucose metabolism, adiponectin has anti-atherogenic [79–82], anti-inflammatory [82,113,116,120] and angiogenic [84,98] properties.

This unique combination of biological properties prompted many investigators to assess plasma concentration of adiponectin during normal and abnormal pregnancy. The hypothesis that adiponectin may play a role in normal and complicated pregnancies is based on several findings: (1) one of the hallmarks of human pregnancy is insulin resistance [11,14,15,16,20,64,66,96]. The conventional view is that this metabolic change is the result of placental hormones such as human placental lactogen (LPL) [5,54,55,95]; however, during recent years, adipokines, including adiponectin, have been implicated in the physiology of insulin resistance during pregnancy [16,60,67,73,92]; (2) lower concentrations of adiponectin have been consistently reported in patients with gestational diabetes as compared to patients with normal pregnancy [3,58,91,104,113,115]. Moreover, pregnant patients with low concentrations of adiponectin during the first trimester are more likely to develop gestational diabetes compared to those with normal concentrations of this hormone [112]; and (3) preeclampsia is associated with insulin resistance, an exaggerated systemic maternal inflammatory response and an anti-angiogenic state, all known to be associated with decreased concentrations of adiponectin. Interestingly, there is inconsistency in the literature regarding the association between

adiponectin and preeclampsia and both higher [40,41,53,68,77,90] and lower [19,22,103] plasma/serum concentrations than those of normal pregnant women have been reported.

The clinical implications of the findings that plasma adiponectin concentrations relate to both physiological and pathological changes of pregnancy are hampered by the lack of knowledge regarding normal adiponectin concentrations throughout pregnancy. We performed this study to determine whether plasma adiponectin concentrations change during normal pregnancy. In addition, we explored the relationships between plasma adiponectin in normal and overweight pregnant patients as well as between non-pregnant and pregnant women.

Materials and methods

Study design and population

A retrospective, nested case-control study was conducted using samples and data retrieved from the bank of biological samples and clinical database of the Perinatology Research Branch of NICHD. The following two groups of subjects were included: (1) normal pregnant women and (2) non-pregnant women. The inclusion criteria for normal pregnant women were: (1) singleton gestation, (2) no prior diabetes mellitus or other metabolic conditions, (3) no obstetrical, maternal or fetal complications during pregnancy, (4) normal plasma glucose concentrations in the first trimester, (5) normal oral glucose tolerance test in the third trimester and (6) delivery at term of a healthy neonate with a birthweight adequate for gestational age (between 10th and 90th percentile). Pregnant women were classified by the gestational age at sample collection and their first trimester body mass index (BMI): normal weight (BMI<25) and overweight (BMI≥25). The non-pregnant women had no prior or current medical or metabolic conditions and were not using oral contraceptives. Written informed consent was obtained from all participants prior to the collection of maternal blood samples. The study was approved by the Institutional Review Board.

Sample collection and human adiponectin immunoassays

Maternal blood samples were collected once from each woman. The gestational ages of sample collection were 11–14 weeks, 15–18 weeks, 19–22 weeks, 23–26 weeks, 27–29 weeks, 31–34 weeks and >37 weeks. Blood samples from non-pregnant women were obtained during the secretory phase of the menstrual cycle. Blood was collected in vials containing ethylenediaminetetra-acetic acid, centrifuged at 1300 × g for 10 min at 4. The plasma obtained was stored at –80 until analysis.

Plasma adiponectin concentrations were determined with the Human Adiponectin ELISA (LINCO Research Inc, St Charles, MO, USA) according to the instructions of the manufacturer. The sensitivity of the assay was 0.91ng/mL, and the coefficients of intra-and inter-assay variation were 4.6% and 6.6%, respectively.

Normal parameters for BMI were defined as <25 according to the definitions of the World Health Organization [24]. Pregnant women were classified by their first trimester body mass index (BMI) into two groups: normal weight (BMI<25) and overweight (BMI≥25) and by the gestational age at sample collection.

Many of these samples have been used previously to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concentrations in non-pregnant women, normal pregnant women and those with pregnancy complications.

Statistical analysis

The Body Mass Index (BMI) was calculated according to the formula: weight (Kg)/height (m)².

Plasma adiponectin concentrations were not normally distributed. Non-parametric methods were used to perform the statistical analysis. Correlation between adiponectin and gestational age was conducted with the Spearman's rank correlation. Multiple of the median comparison of adiponectin among gestational age groups was performed by Kruskal Wallis with post hoc analyses by Mann Whitney *U*-test with Bonferroni adjustment for the calculated P-value in order to maintain the significance level at 0.05. Analysis of covariance (ANCOVA) was performed to control for confounding factors that could affect plasma adiponectin changes during pregnancy such as maternal age, BMI, and time of sample storage.

A reference table showing the normal plasma adiponectin concentrations in each gestational age group as well as for non-pregnant women was constructed with the 10th, 25th, 50th, 75th, and 90th percentiles.

Results

Forty non-pregnant women, 400 pregnant women of normal-weight (BMI < 25) and 277 overweight (BMI ≥ 25) pregnant women were included in the study. Maternal age, first trimester weight, first trimester BMI and plasma adiponectin concentrations were not significantly different between non-pregnant and pregnant women of normal weight. Among pregnant women there were no significant differences in maternal age, parity, gestational age at delivery between those with normal weight and overweight women. Maternal characteristics and plasma adiponectin concentrations, according to gestational age at sampling for every gestational age group for normal as well as for overweight pregnant women, are summarized in Tables 1A and 1B, respectively, as well as in Figure 1.

Plasma adiponectin concentrations in non-pregnant women

Adiponectin concentrations were measurable in all cases, at every gestational age group. During pregnancy, the range of adiponectin concentrations were between 2.7 µg/mL and 25.0 µg/mL, while in non-pregnant women, the range was between 3.5 µg/mL and 22.4 µg/mL. When all pregnant women were pooled together, plasma adiponectin concentrations in non-pregnant women were not significantly different in the first trimester. However, pregnant women of normal weight at 11–14 weeks and 15–18 weeks of gestation had a higher median plasma adiponectin concentration than that of non-pregnant women. No differences in plasma adiponectin concentration were detected between non-pregnant and overweight pregnant women at any gestational age.

The overall analysis of all pregnant women showed a slight but statistically significant decrease of plasma adiponectin concentrations with advancing gestation (Spearman's rho: -0.112; P=0.003). A significant difference was found between the first and the third trimesters.

Comparison between maternal adiponectin in normal weight and overweight pregnant women

The median plasma adiponectin concentration in overweight pregnant women was significantly lower than that of those with normal weight (median 7.4 µ/mL 2.76–22.38 vs. 8.87 µ/mL 2.77–25.03, respectively, P<0.05). (Figure 1). Plasma adiponectin concentrations were significantly lower in overweight women than in women of normal weight between 11–14 weeks (median: 7.9 µ/mL, range: 2.7–16.4 vs. median: 10.2 µ/mL, range: 4.6–22.1, respectively, P<0.003), 19–22 weeks (median: 6.5 µ/mL, range: 4.1–18.7 vs. median: 9.0 µ/

mL, range: 4.2–17.9, respectively, $P<0.001$), 23–26 weeks (median: 6.7 μmL , range: 3.9–16.5 vs. median: 8.6 μmL , range: 3.8–19.4, respectively, $P<0.01$) and after 37 weeks (median: 7.2 μmL , range: 2.8–19.2 vs. median: 8.6 μmL , range: 3.3–17.4, respectively, $P<0.002$).

During pregnancy, plasma adiponectin concentrations of women with normal weight showed a slight but significant decrease with advancing gestational age (Spearman's ρ : -0.14 ; $P=0.004$). In contrast, no correlation was found between plasma adiponectin concentrations and gestational age in overweight pregnant women.

Tables containing the reference values of plasma adiponectin concentrations in pregnant women of normal weight ($\text{BMI}<25$) as well as overweight ($\text{BMI}>25$) were constructed (Tables 2A and 2B, respectively) including the 10th, 25th, 50th, 75th and 90th percentiles for each gestational age group.

Analysis of covariance (ANCOVA) was used to control for potential confounding factors of adiponectin concentration in pregnancy. The covariates that were included in the model were maternal age, time of sample storage, gestational age, BMI and parity. Gestational age significantly contributed to the changes of plasma adiponectin concentrations during pregnancy.

Discussion

Principal findings of the study

(1) Maternal plasma adiponectin was detectable in all patients; (2) when normal and overweight pregnant women were pooled together there were no significant differences between pregnant and non-pregnant women in median plasma adiponectin concentrations. However, the median plasma adiponectin concentration was higher in pregnant of normal weight than in non-pregnant women in two gestational age categories (11–14 and 15–18 weeks of gestation). These differences were not observed between non-pregnant and overweight pregnant women at any gestational age; (3) Plasma adiponectin concentrations showed a significantly negative correlation with advancing gestational age; and (4) overweight patients had significantly lower adiponectin concentrations than did normal weight women, and this difference was consistent in the first, second, and third trimesters.

Maternal plasma adiponectin in normal human pregnancy

Most of the literature regarding maternal adiponectin is confined to comparisons between normal pregnant women and patients with obstetrical complications such as gestational diabetes [3,58,91,104,113,115] and preeclampsia [19,22,40,41,53,68,77,90,103]. Indeed, there is a relative paucity of scientific data regarding the association between non-pregnant and pregnant women, no normogram based on a large sample size is currently available. The results reported herein are in agreement with a previous study by Cseh et al. in which maternal plasma adiponectin concentrations were significantly lower in third trimester ($n=15$) than in the first trimester ($n=13$) [21]. The same findings have been reported in longitudinal studies by Catalano et al. ($n=10$) [16] and Fuglsang et al. ($n=11$) [34]. The latter reported that the lowest concentrations of maternal serum adiponectin can be found during the third trimester, and that there are no significant differences in maternal serum adiponectin concentrations between non-pregnant and pregnant women. In addition, Naruse et al. [77] and Suwaki et al. [103] reported no significant difference in serum adiponectin concentrations between non-pregnant and pregnant women. Moreover, no significant correlation between serum adiponectin concentrations and advancing gestational age was found by Naruse et al. [77] and Suwaki et al. [103]. Differences in study design and sample size may account for this disparity.

Why does the concentration of adiponectin decrease with advancing gestation?

We observed a negative correlation between maternal plasma adiponectin concentrations and gestational age. Several explanations may account for this finding. It has been proposed that adiponectin is associated with insulin resistance [7,33,39,44,111,118,123]. Recently, several observations suggested that this concept holds true for human pregnancy. Indeed, maternal adiponectin concentrations correlate with insulin resistance indices during pregnancy [16,67,73,92]. Moreover, low concentrations of adiponectin in early pregnancy were associated with increased risk for development of gestational diabetes [112]. Taken together, these findings suggest a key role for adiponectin in the regulation of insulin resistance during pregnancy, as well as in the pathophysiology of gestational diabetes.

An alternative possibility is the effect of quantitative and qualitative changes in adipose tissue during pregnancy. Pregnancy is characterized not only by increased body weight, but also by a remarkable increased fat deposit [12,13,26,48,59,89]. Moreover, although scarce, there is evidence to support that visceral fat deposits increase during pregnancy [26,59]. Interestingly, although adiponectin is secreted by adipose tissue, an increase in fat mass leads to down-regulation of adiponectin [2], whereas body weight reduction results in elevation of adiponectin concentrations [27,119]. Similarly, increased concentrations of this adipokine were found in anorexic patients whose fat mass is markedly decreased [23,27,45,74,87]. These findings suggest that adipose tissue may exert a negative feedback on adiponectin production. Several studies have demonstrated that adiponectin expression is reduced in hypertrophic adipocytes upon increase in triglyceride content [63,117,122]. Furthermore, these studies have indicated that the levels of expression of adiponectin may be more closely related to adipocyte size and stage of differentiation rather than to total adipose tissue mass. This hypothesis is supported by reports that have demonstrated a prominent increase in adiponectin concentration in subjects who were treatment with peroxisome proliferator-activated receptor- γ agonists like troglitazone, which distinctly increase the number of newly differentiated small adipocytes, in conjunction with body weight gain [88,121]. Thus, high fat mass and adipocyte hypertrophy in pregnant women adipose tissue may explain the decrease in concentrations of adiponectin along pregnancy.

Why is the maternal plasma concentration of adiponectin lower in overweight than in normal weight pregnant women?

Similarly to obesity, human pregnancy is characterized by increased body weight, high adipose tissue deposition as well as elevated concentrations of various adipokines. We investigated the relative contribution of obesity to maternal adiponectin concentrations by comparing plasma concentrations of this hormone in normal weight and overweight pregnant women. Predictably, median adiponectin concentrations were significantly lower in overweight pregnant women when compared with normal weight pregnant women. Interestingly, while plasma concentrations of adiponectin were negatively correlated with gestational age in normal weight pregnant women, the decrease was blunted in the overweight pregnant women. Our data do not allow us to dissect cause and effect in the relationship between obesity, pregnancy and plasma adiponectin; however, we propose that the differences between normal and overweight pregnant women may result from alterations in insulin resistance and from the effects of excess adipose tissue. The lack of association between plasma adiponectin and gestational age in overweight pregnant women suggests that the excess adipose tissue exerts its maximal negative feedback on adiponectin concentrations early in pregnancy. Thus, both additional weight gain during gestation and pregnancy-induced insulin resistance have only marginal effects in this subset of patients, in contrast to normal weight pregnant women.

Why are there no differences in maternal plasma adiponectin between pregnant and non-pregnant women?

When all pregnant women were pooled together, there were no differences between pregnant and non-pregnant women in the median plasma adiponectin concentrations. When the analysis of the data was confined only to normal weight patients, pregnant women had higher median, plasma concentrations of adiponectin between 11–14 weeks and 15–18 weeks compared with non-pregnant women. Interestingly, no differences were detected between non-pregnant and overweight women at any gestational age. Adiponectin expression and secretion have been shown to be affected by a myriad of factors. Regulation of plasma adiponectin during pregnancy is further complicated since there is a paucity of scientific data in regards to whether, and to what extent, the hormonal and metabolic alterations during pregnancy may affect adiponectin concentrations. In addition to insulin resistance and obesity, several adipokines, hormones and peptides have been implicated in regulation of adiponectin including: TNF- α , IL-6 [30,37], glucocorticoids [37], insulin [10,17,97], estrogen [18,25,36], testosterone [36, 85,86], prolactin [18,78] and others. Of note, inconsistency in the literature with regard to the effect of these factors on adiponectin plasma concentrations as well as contradictory effects of these regulators on adiponectin contributes to the uncertainty. Thus, regulation of maternal plasma adiponectin concentrations is complex.

In conclusion, this demonstrates that adiponectin is a physiological component of maternal plasma during pregnancy and that there were no differences between pregnant and non-pregnant women in the median plasma adiponectin concentrations. Moreover, were able to further clarify the association between adiponectin, pregnancy and overweight by demonstrating that overweight pregnant women had significantly lower plasma adiponectin concentrations than those with normal weight, and by observing a negative correlation with gestational age only in normal weight women. The report of this study as well as the normogram herein presented; should be beneficial to those investigating the intriguing relationships between adiponectin, pregnancy and the mechanisms of metabolic alterations in normal and abnormal pregnancies.

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Figure 1. Plasma adiponectin concentrations in normal (BMI < 25) and overweight (BMI ≥ 25) pregnant women, according to gestational age groups.

Table 1A. Demographic and clinical characteristics of normal weight pregnant women (BMI<25) and plasma adiponectin concentrations according to gestational age at sampling.

	11-14 weeks (n=50)	15-18 weeks (n=50)	19-22 weeks (n=50)	23-26 weeks (n=50)	27-29 weeks (n=50)	31-34 weeks (n=50)	>37 weeks (n=100)
Maternal age (median, range; years)	24 (16-39)	26 (17-41)	26 (16-38)	24 (15-41)	25 (17-42)	26 (17-39)	24 (15-38)
GA at delivery (median, range; weeks)	40.0 (37-42)	39.7 (37-42)	39.7 (37-42)	39.5 (37-42)	39.7 (38-41)	40.0 (37-42)	39.7 (37-42)
BMI at 1st trimester (median, range; kg/m ²)	22.6 (17.3-24.8)	21.9 (17.8-24.8)	21.6 (17-24.8)	22.3 (19.1-24.9)	22.0 (16.8-24.4)	22.6 (13.1-24.7)	22.3 (16.2-24.9)
Adiponectin (median, range; µg/mL)	10.2 (4.6-22.1)*	9.4 (3.8-19.3)*	9.0 (4.2-17.9)	8.6 (3.8-19.4)	8.3 (2.9-18.9)	8.2 (2.7-14.4)*	8.6 (3.31-17.4)

	11-14 Weeks (n=37)	15-18 Weeks (n=32)	19-22 Weeks (n=34)	23-26 Weeks (n=31)	27-29 Weeks (n=35)	31-34 Weeks (n=35)	>37 Weeks (n=72)
Maternal age (median, range; years)	27 (16-40)	26 (15-41)	27 (20-38)	30 (20-43)	30 (19-42)	26 (18-43)	28 (15-43)
GA at delivery (median, range; weeks)	39.2 (37-41)	40.0 (37-42)	39.7 (37-42)	39.8 (37-42)	40.0 (37-42)	39.4 (38-42)	39.7 (38-42)
BMI at 1st trimester (median, range; kg/m ²)	27.5 (25.0-36.9)	26.2 (25.0-35.1)	27.8 (25.0-34.4)	27.3 (25.0-36.7)	27.4 (25.0-40.0)	26.8 (25.0-36.3)	27.4 (25.0-40.1)
Adiponectin (median, range; µg/mL)	7.95 (2.7-16.4)	8.26 (3.8-22.3)	6.5 (4.1-18.7)	6.7 (3.9-16.5)	7.5 (2.9-14.3)	6.5 (3.7-12.7)	7.2 (2.8-19.2)

BMI: Body Mass Index; GA: Gestational Age

* The significant differences shown by post hoc analysis were: [11-14 weeks / 31-34 weeks] P = 0.022; [15-18 weeks / 31-34 weeks] P = 0.007.

Table 2A. Plasma adiponectin concentrations (µg/mL) in normal weight (BMI<25) pregnant women.

	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
11–14 weeks	5.6	7.7	10.2	12.9	17.4
15–18 weeks	4.8	7.6	9.5	11.9	14.8
19–22 weeks	5.7	7.2	9.0	11.5	14.6
23–26 weeks	5.6	7.2	8.6	10.8	14.1
27–29 weeks	4.2	6.4	8.3	10.9	12.2
31–34 weeks	4.6	5.5	8.2	10.4	12.2
>37 weeks	5.0	6.7	8.6	11.3	13.4

Table 2B. Plasma adiponectin concentrations (µg/mL) in overweight (BMI>25) pregnant women.

	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
11–14 weeks	4.2	6.2	7.9	9.7	11.9
15–18 weeks	5.3	7.1	8.2	11.2	16.1
19–22 weeks	4.3	5.4	6.5	8.4	12.2
23–26 weeks	4.8	5.7	6.7	9.5	12.4
27–29 weeks	4.3	4.6	7.5	9.7	13.9
31–34 weeks	4.9	5.6	6.5	8.3	9.6
>37 weeks	5.1	6.0	7.2	9.1	11.3

BMI: Body Mass Index